# PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

X/16418

# PCT

## WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing
*(day/month/year)* see form PCT/ISA/210 (second sheet)

18 JUL 2005

Applicant's or agent's file reference
see form PCT/ISA/220

**FOR FURTHER ACTION**
See paragraph 2 below

| International application No. | International filing date *(day/month/year)* | Priority date *(day/month/year)* |
|---|---|---|
| PCT/US2004/025591 | 25.08.2004 | 27.08.2003 |

International Patent Classification (IPC) or both national classification and IPC
A61P25/00, A61K31/5375, A61K31/138, A61K31/4468, A61K31/538, A61K31/5415, A61K31/40, A61K31/439,

Applicant
ELI LILLY AND COMPANY

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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**WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US2004/025591

**Box No. I Basis of the opinion**

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

**Box No. II Priority**

1. ☒ The following document has not been furnished:

   ☒ copy of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(a)).

   ☐ translation of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(b)).

   Consequently it has not been possible to consider the validity of the priority claim. This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. ☐ The International Searching Authority has not been able to consider the validity of the priority claim because a copy of the earlier application whose priority has been claimed was not available to the International Searching Authority at the time that the search was conducted (Rule 17.1). This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

4. Additional observations, if necessary:

**Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 1,3 (I.A. only)

because:

☒ the said international application, or the said claims Nos. 1,3 (I.A. only) relate to the following subject matter which does not require an international preliminary examination *(specify)*:

**see separate sheet**

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the whole application or for said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

| | | |
|---|---|---|
| the written form | ☐ | has not been furnished |
| | ☐ | does not comply with the standard |
| the computer readable form | ☐ | has not been furnished |
| | ☐ | does not comply with the standard |

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

**Box No. IV Lack of unity of invention**

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has:

   ☐ paid additional fees.

   ☐ paid additional fees under protest.

   ☒ not paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is

   ☐ complied with

   ☒ not complied with for the following reasons:

   **see separate sheet**

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☐ all parts.

   ☒ the parts relating to claims Nos. 1,2 (in part), 3

**Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

| | | | |
|---|---|---|---|
| Novelty (N) | Yes: | Claims | |
| | No: | Claims | 1-3 |
| Inventive step (IS) | Yes: | Claims | |
| | No: | Claims | 1-3 |
| Industrial applicability (IA) | Yes: | Claims | 2 |
| | No: | Claims | 1,3 |

2. Citations and explanations

   **see separate sheet**

**Re Item III**

**Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

Claims 1 and 3 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

The very broad definition "communication disorder" does not appear to be a term frequently used in the art and is considered to lack clarity (Art. 6 PCT). Moreover, the claims do not find any support in the description, as no substantiated data demonstrating the claimed therapeutic effect is provided (Art. 6 PCT).

**Re Item IV**

**Lack of unity of invention**

The current application is directed to the problem of providing alternative pharmaceutical agents for treating stuttering or other communication disorders. The different norepinephrine reuptake of generic formulae (I)-(IG) are related by possessing a norepinephrine reuptake inhibitory activity.
The concept of treating communication disorders using norepinephrine reuptake inhibitors is however known from documents D1-D3. The unifying concept is therefore not novel. The application, hence does not meet the requirements of unity of invention as defined in Rules 13.1 and 13.2 PCT.
The groups of claims are directed to different solutions to the problem.

This Authority considers that there are 5 inventions covered by the claims indicated as follows:

I: Claims 1, 2 (in part), 3 directed to the use of a norepinephrine reuptake inhibitor selected from atomoxetine or a compound of formula (I) in the treatment of stuttering or another communication disorder.

II: Claims 1, 2 (in part) directed to the use of a norepinephrine reuptake inhibitor selected from reboxetine or a compound of formula (IB), (IC) or (IG) in the treatment of stuttering or another communication disorder.

III: Claims 1, 2 (in part) directed to the use of a norepinephrine reuptake inhibitor of

formula (IA) in the treatment of stuttering or another communication disorder.

IV: Claims 1, 2 (in part) directed to the use of a norepinephrine reuptake inhibitor of formula (ID) in the treatment of stuttering or another communication disorder.

V: Claims 1, 2 (in part) directed to the use of a norepinephrine reuptake inhibitor of formula (IE) or (IF) in the treatment of stuttering or another communication disorder.

Only the first group (group I as above) was subject to an International Search (cf. also reasoning on the separate sheet of the International Search Report).
The Applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no International Search Report has been established need not be the subject of an International Preliminary Examination (Rule 66.1(e) PCT). For this reason, the discussion that follows is limited to the subject-matter of group I.

**Re Item V**

**Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

Reference is made to the following documents:

D1: US 2003/087963 A1 (CURRIE MARK G ET AL) 8 May 2003 (2003-05-08)
D2: US-B-6 323 2421 (MUELLER PETER STERLING) 27 November 2001 (2001-11-27)
D3: US 2002/052340 A1 (MCCULLOUGH JOHN R ET AL) 2 May 2002 (2002-05-02)
D4: EP-A-0 756 869 (LILLY CO ELI) 5 February 1997 (1997-02-05)
D5: EP-A-0 919 235 (LILLY CO ELI) 2 June 1999 (1999-06-02)

**Novelty - Article 33(2) PCT**

D2 (US63232421) discloses the treatment of speech and communication disorder with norepinephrine reuptake inhibitor Sibutramine.

D3 (US2002052340) discloses Bupropion as an inhibitor of norepinephrine reuptake for treating disorders ameliorated by inhibition of neuronal monoamine reuptake, e.g. speech disorders. D1 (US2003087963) describes Sibutramine for treating such disorders. Also disclosed in D1 are pharmaceutical combinations with e.g. tomoxetine.

D4 (EP0756869) discloses compounds of formula (I) as norepinephrine uptake

inhibitors in the treatment of attention-deficit/hyperactivity disorder.

D5 (EP0919235) discloses norepinephrine reuptake inhibitor of formula (I), including tomoxetine, and (R)-N-methyl-3-(2-methylthio -phenoxy)-3-phenylpropylamine, to be used in the treatment of conduct disorder such as Attention-deficit Hyperactivity Disorder (ADHD).

**Novelty - Article 33(2) PCT**

ADHD has to be considered to fall under the unclear term "communication disorder" (cf. comment under Item III above). Hence, D5 destroys novelty for claims 1-3.
D1 also has to be considered novelty-destroying for the subject matter of claims 1-3, as pharmaceutical combinations active against speech disorder comprising tomoxetine are disclosed.

**Inventive Step - Article 33(3) PCT**

An inventive step can only be assessed when the Applicant has established novelty for the independent claims.
It is however noted that no substantiated data is provided that demonstrates the existence of the claimed therapeutic use.
Moreover, it appears obvious to expect an effect of the known norepinephrine reuptake inhibitors of formula (I) and atomoxetine against communication disorders, as norepinephrine reuptake inhibitor were known in the treatment of speech disorder.

**Industrial Applicability - Article 33(4) PCT**

For the assessment of the present claims 1-3 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.